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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 27 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

**SUBJECT** **TRIISOPROPANOLAMINE SALT OF 2,4-D:** Generic Data Submission As Required in the Registrations Standard.

**FROM:** Jess Rowland, Toxicologist 3/11/92.
Section II, Toxicology Branch II
Health Effects Division (H7509C)

**TO:** W. Waldrop / J. Coombs
Product Manager (71)
Reregistration Division

**THRU:** K.Clark Swentzel, Section Head 8/17/9
Section II, Toxicology Branch II
Health Effects Division (H7509C)
and
Marcia van Gemert, Ph.D., Chief 8/17/92
Toxicology Branch II
Health Effects Division (H7509C)

**TASK IDENTIFICATIONS: Submission: S414835 BARCODE: D176189**

**Caswell No. 315 AE PCCODE: 030035**

**ACTION REQUESTED:** Review of a general metabolism study [85-1] for the Triisopropanolamine salt of 2,4-D [2,4-D-TIPA].

**SUMMARY:** In this study, male Fischer 344 rats received a single oral dose of a solution providing targeted doses of 10 mg 2,4-D/kg and 10.7 mg $^{14}$C-TIPA/kg. $^{14}$C-TIPA was rapidly absorbed by the gastrointestinal tract and excreted in the urine as unchanged TIPA. The concentration of radioactivity in the plasma peaked 0.25 hr post-dosing and then decreased in a tri-exponential manner. Rapid elimination of $^{14}$C-TIPA resulted in no accumulation in the tissues; less than 1% of the administered radioactivity remained in the tissues and carcass 72 hrs post-dosing. $^{14}$C-TIPA did not undergo extensive metabolism. Essentially all radioactivity excreted in the urine represented unchanged $^{14}$C-TIPA.



10818

Urinary excretion was the major route of excretion with 80% of the dose being excreted by the first 24 hr post-dosing period. Fecal excretion accounted for 4-7% of the dose, expired $^{14}CO_2$ accounted for 3-4%, and the final cage rinse about 1% of the dose. The proportion of 2,4-D excreted during the first 12 hr post-dosing in this study was almost identical to the proportion of 2,4-D excreted by male rats given a single 1 mg/kg oral dose of $^{14}C$-2,4-D acid in a previous study [MRID No.417373-02]. Results indicate that: $^{14}C$-TIPA is well absorbed and rapidly excreted in the urine primarily as the unchanged compound; does not accumulate in rat tissues; and the excretion of the parent acid, 2,4-D is not affected by the addition of the triisopropanolamine salt at the dose level used in this study. Apparently although this study characterized the single dose pharmacokinetics of the test material, the standard protocol for a metabolism study was not followed [i.e., only one dose was tested instead of two doses, did not employ repeated dose regimen, and determination of radioactivity in tissues] as specified in guideline 85-1. Therefore, this study is classified as unacceptable.

**CORE CLASSIFICATION: Unacceptable;** this study does not satisfy the guideline requirement 85-1 for a general metabolism study with the 2,4-D-TIPA.

**PRIMARY REVIEWER:** Jess Rowland, Toxicologist
Section II, Toxicology Branch II

**SECONDARY REVIEWERS:** K. Clark Swentzel, Section Head
Section II, Toxicology Branch II

Alberto Protzel, Pharmacologist
Section III, Toxicology Branch II

**DATA EVALUATION REPORT**

**STUDY TYPE:** General Metabolism **GUIDELINE: 85-1**

**CASWELL NO. 315 AE MRID No. 422203-01 HED PROJECT No. 2-1848**

**TEST MATERIAL: TRIISOPROPANOLAMINE** Salt of 2,4-D ACID **[2,4-D TIPA]**

**REGISTRANT:** DowElanco, Indianapolis, IN.

**TESTING LABORATORY:** The Toxicology Research Laboratory, Michigan

**STUDY IDENTIFICATION:** K-008866-013

**TITLE OF REPORT:** *2,4-DICHLOROPHENOXYACETATE,TRIISOPROPANOLAMINE SALT; DISSOCIATION AND METABOLISM STUDY IN MALE FISHER 344 RATS.*

**AUTHOR(S):** M.D. Dryzga, G.A. Bormett and R.J. Nolan

**REPORT DATE:** January 31, 1992

**SUMMARY:** In this study, male Fisher 344 rats received a single oral dose of a solution providing targeted doses of 10 mg 2,4-D/kg and 10.7 mg $^{14}$C-TIPA/kg. $^{14}$C-TIPA was rapidly absorbed by the gastrointestinal tract, and excreted in the urine as unchanged TIPA. The concentration of radioactivity in the plasma peaked 0.25 hr post-dosing and then decreased in a tri-exponential manner. Due to its rapid elimination, $^{14}$C-TIPA did not accumulate in the tissues; less than 1% of the administered radioactivity remained in the tissues and carcass in rats sacrificed 72 hr post-dosing. $^{14}$C-TIPA did not undergo extensive metabolism. Essentially all radioactivity excreted in the urine represented unchanged $^{14}$C-TIPA. Urinary excretion was the major route with 80% of the dose being excreted by the first 24 hr post-dosing period. Fecal excretion accounted for 4-7% of the dose, expired $^{14}CO_2$ accounted for 3-4%, and the final cage rinse about 1% of the dose. Results indicate that, $^{14}$C-TIPA is well absorbed and rapidly excreted in the urine primarily as the unchanged compound, does not accumulate in rat tissues, and the excretion of the parent acid, 2,4-D is not affected by the addition of the TIPA salt.

## I. INTRODUCTION

This Data Evaluation Report summarizes the experimental procedures and results of a general metabolism study.

## II. MATERIALS AND METHODS

### 1. Test Material

Common Name: Trisopropanolamine Salt of 2,4-D

Radioactive: Triisopropanolamine-1-$^{14}$C-
Radiochemical purity: 97.5 ± 1.1%
Specific activity: 31.9 mCi/mmol
Lot No. GHD 1345-56a

Nonradioactive: 2,4-D TIPA
72.2%, technical
38.7%, acid equivalent
Lot No. AGR #0276428

### 2. Test Animals

Species: Rats
Strain: Fisher 344
Sex: Male
Age: 10 weeks
Weight: 170 - 183 g
Identification: Ear tags
Acclimation: 1-week
Housing:Individual Roth-type metabolism cages
Food: Certified rodent chow #5002 ad libitum
Water: Tap water ad libitum
Environment: Temperature/Humidity/Photocycle controlled

### 3. Study Design:

This study was designed to characterize the absorption, distribution, excretion and biotransformation of $^{14}$C-TIPA salt of 2,4-D in male rats following a single oral dose. The expired air was collected to determine whether significant amounts of $^{14}$C would be eliminated in the expired air of treated animals.

The amounts of radioactivity, 2,4-D and TIPA administered to rats are summarized in Table 1.

4. Test Material Formulation

The dose solution was prepared by adding a measured volume of $^{14}$C-TIPA. Then a measured volume of non-radiolabeled 2,4-D TIPA was added and diluted with distilled water. Target concentrations of TIPA, 2,4-D and radioactivity in this solution was 5.35 mg TIPA, 5 mg 2,4-D and 60 µCi of $^{14}$C per ml. Radioactivity in the dose solution was quantified using a liquid scintillation counter. In addition, analyses of three 100 µl aliquots of the dose solution showed 5.63 mg 2,4-D/mL. The concentration of TIPA in the dose solution was calculated to be 5.55 mg/mL based on the amount of 2,4-D [5.18 mg TIPA/mL;molar ratio of 2,4-D to non-radiolabeled TIPA was 0.92] and $^{14}$C-TIPA [0.37 mg/mL] in the dose solution.

5. Treatment

The rats were weighed and based on their body weight a measured volume of the dose solution was administered by gavage. The quantity of the dose solution was determined by weighing the syringe prior to and following dosing [see Table 1]. Administration of the dose solution at the rate of 2 mL/kg resulted in a targeted dose of 10.7 mg TIPA and 10 mg, 2,4-D/kg body weight and 20-30 µCi of $^{14}$C per animal.

6. Experimental Procedures

Blood was collected from each rat at 0.25, 0.5, 0.75, 1, 1.5, 2,4, 6, 8, 12, 18, 24, 48 and 72 hr post-dosing, and plasma was analyzed for radioactivity

Urine was collected in dry-ice chilled containers that were changed at 6, 12, 24, 48 and 72 hours post-dosing, and was analyzed for radioactivity. The urine and cage rinse radioactivity was combined for each collection interval and expressed as radioactivity excreted in the urine.

Feces was collected at 24-hour intervals in dry-ice chilled containers, and analyzed for radioactivity.

Expired air was passed through a charcoal trap to capture expired organic $^{14}$C and then through a monoethanolamine: 1-methoxy-2-propanol trap to capture expired $^{14}CO_2$. Due to insufficient radioactivity to quantify [< twice background] during the 0-12 hour collection period, the collection using charcoal traps was discontinued. The $^{14}CO_2$ traps were changed at 12, 24, 36, 48 and 72 hours post-dosing and analyzed for radioactivity.

Tissue samples collected and analyzed for radioactivity from animals sacrificed 72 hours post-dosing were: liver, kidneys, perirenal fat, skin and remaining carcass.

$^{14}C$ radioactivity was quantified with a Beckman LS3801 liquid scintillation counter.

Metabolite characterization studies were performed with pooled urine samples collected during the first 12 hours [0-6 and 6-12 hr] post-dosing. Gas chromatography / mass spectrometry analysis was employed for quantification of derivatives of urinary 2,4-D and urinary $^{14}C$-TIPA, and characterization of $^{14}C$-TIPA metabolites.

7. Regulatory Compliance

A signed Statement of No Confidentiality Claim was provided that was dated January 17, 1992.

A signed Statement of Compliance with EPA's GLP was provided that was dated January 17, 1992.

A flagging statement per 40 CFR. 158.34 indicated that the criteria for flagging studies does not apply to this study; this was dated January 31, 1992.

A signed Quality Assurance Statement was dated January 31, 1992. This date conforms to the review of the study phases and the draft and the final reports.

## III. RESULTS

### 1. Adequacy of Dosing

The amount of 2,4-D, TIPA and radioactivity each animal received are summarized in Table 1. The average amounts of 2,4-D [11.4 mg/kg], and TIPA [11.2 mg/kg] administered were within 7% and 12% of the targeted dose of 2,4-D [10.7 mg/kg] and TIPA [10 mg/kg], respectively. The amount of radioactivity [22 μCi/rat] was within the targeted range [20-30 μCi/rat].

### 2. Absorption

Concentration of $^{14}$C-TIPA in the plasma at various intervals are summarized in Table 2. Orally administered $^{14}$C-TIPA was rapidly and extensively absorbed by the gastro-intestinal tract. The rapid absorption was evident since the highest concentration of radioactivity [mean, 4.5 μg eq $^{14}$C-TIPA/g plasma] was detected in the plasma at 0.25 hr post-dosing. The amount of radioactivity detected in the urine and cage rinse thorough 72 hours indicate that a minimum of 83.8% of the administered $^{14}$C-TIPA was absorbed. The concentration of $^{14}$C in the plasma decreased in tri-exponential manner. A 5-fold decrease occurred during the first 4 hr post-dosing period. The peak concentrations were 3% after 24 hr and only 1.3% after 72 hr post-dosing. The half-lives estimated for the rapid initial, middle, and terminal phases were 0.76, 3.6 and 38.5 hr, respectively. The calculated area under the curve [AUC], volume of distribution [$V_d$] and whole body [$CL_T$] and renal clearance [$CL_r$] were 24.03 hr.μg equiv $^{14}$C-TIPA/ g plasma, 1.8 l/kg body weight, and 7.77 and 6.51 ml/min/kg, respectively.

### 3. Distribution

The distribution of radioactivity recovered 72 hours post-dosing are summarized in Table 3. The concentrations of radioactivity in the tissues are summarized in Tables 4 and Table 5. Approximately 95% of the $^{14}$dose was recovered in the urine [84%], feces [5%], $^{14}CO_2$ [4%], tissues/carcass [0.8%], and final cage wash [0.8%] 72 hr post-dosing [Table 3]. Data show that TIPA does not accumulate in the tissues; less than 1% of the administered dose remained in the carcass and tissues 72 hours post-dosing. Concentrations were low in all tissues with the liver containing the greatest concentrations [0.02% of the dose/g wet weight]. The remaining tissues and carcass contained less than 0.01% of the dose/g wet tissue [Tables 4 and 5].

4. Metabolism

The amount of $^{14}$C-TIPA and 2,4-D excreted in the urine is presented in Table 6. GC/MS analysis indicated that $^{14}$C TIPA was rapidly and almost quantitatively excreted unchanged in the urine. Unchanged TIPA accounted for 95% of the radioactivity in the 0-6 hr urine sample and 80% in the 6-12 hr sample. The amount of 2,4-D excreted during the first 12 hr post-dosing [i.e.,70.5% of the dose] is almost identical to the amount of 2,4-D excreted by male rats given a single 1 mg/kg oral dose of $^{14}$C-2,4-D acid [69.3%; MRID No. 417373-02; HED Document No. 008561]. Although the elimination of 3-4% of the administered radioactivity as $^{14}CO_2$ [see below] suggests that $^{14}$C-TIPA undergoes some metabolism, impurities [the radiochemical purity of the radiotracer was 97.5% ± 1.1%] present in the $^{14}$C-TIPA could have accounted for the $^{14}CO_2$.

5. Excretion

Radioactivity excreted in the urine, feces and as $^{14}CO_2$ are presented in Tables 7, 8, and 9, respectively. Following rapid absorption and minimal metabolism, $^{14}$C-TIPA is excreted during the first 24-h post dosing. The principal route of excretion is the urine which contained between 81 and 85% of the dose. Most of the dose [65-70%] was excreted in the urine during the 0-6 h collection interval followed by 9-14% during the 6-12 hr interval. By 24 hr post-dosing, 82.8% of the dose was recovered. Only 1% was excreted between 24 and 72 hr post-dosing. As with the urine, most [84.6%] of the fecal radioactivity was eliminated during the first 24-hr post-dosing. The amount of radioactivity [3-4% of the dose] detected in the 0-12 hr collection interval represented over 86% of the $^{14}CO_2$ excreted during the entire 72 hr post-dosing interval. The amount of $^{14}$C found in the traps for volatile organic was insufficient to quantify.

6. Metabolite Characterization

$^{14}$C-TIPA was eliminated unchanged in the urine; radioactivity attributed to $^{14}$C-TIPA accounted for 95% in the 0-6 hr sample and 80% in the 6-12 hr sample. Mass spectra and extracted ion chromatograms for the derivatized urine extract and TIPA standard were identical [see appended Figures 3,4 of the report].

## III. DISCUSSION

Following a single oral administration to male rats, $^{14}$C-TIPA is rapidly and extensively absorbed by the gastrointestinal tract, and rapidly excreted in the urine as unchanged TIPA. The concentration of radioactivity in the plasma peaked 0.25 hr post-dosing and then decreased in a tri-exponential manner. Due to its rapid elimination, $^{14}$C-TIPA did not accumulate in the tissues; less than 1% of the administered radioactivity remained in the tissues and carcass when the rats were sacrificed 72 hrs post-dosing. $^{14}$C-TIPA did not undergo extensive metabolism. Essentially all radioactivity excreted in the urine represented unchanged $^{14}$C-TIPA. The proportion [70.5%] of 2,4-D excreted in the urine during the 0-12 hr dose interval was comparable to that [69.3%] excreted in the same time interval in another study [MRID No. 417373-02; HED Document No. 008561] in which the administered dose to male rats was 1 mg/kg of $^{14}$C-2,4-D acid. The major route of excretion was the urine with 80% of the dose excreted by the first 24 h post-dosing period. The feces accounted for only 4-7% of the dose. Expired $^{14}CO_2$ accounted for 3-4% and the final cage rinse was about 1% of the dose.

## IV. CONCLUSION

This study demonstrates that orally administered $^{14}$C-TIPA is well absorbed and rapidly excreted in the urine primarily as the unchanged compound, is not accumulated in rat tissues, and the excretion of the parent acid, 2,4-D is not affected by the addition of the triisopropanolamine salt at the dose level used in this study. Apparently, although this study characterized the single dose pharmacokinetics of the test material, this study did not follow the standard protocol for a metabolism study [i.e., only one dose was tested instead of two dose levels, did not employ repeated dosing regimen, and determination of radioactivity in tissues] as specified in guideline 85-1. Therefore, this study is classified as unacceptable.

## V. CORE CLASSIFICATION

**Unacceptable;** this study does not satisfy guideline requirement 85-1 for a general metabolism study.

**Table 1. Amount of Radioactivity, 2,4-D and TIPA Administered in a Single Oral Dose to Male Rats.**

| Animal No. | Body Weight [kg] | Syringe Weight Full [g] | Syringe Weight Empty [g] | Net [g] | dpm[a] | 2,4-D[b] [mg] | 2,4-D [mg/kg] | TIPA[c] [mg] | TIPA [mg/kg] |
|---|---|---|---|---|---|---|---|---|---|
| 90A-7594 | 0.1705 | 7.0984 | 6.7478 | 0.3506 | 47862067 | 1.974 | 11.6 | 1.946 | 11.4 |
| 90A-7599 | 0.1831 | 7.1200 | 6.7493 | 0.3707 | 50606013 | 2.087 | 11.4 | 2.057 | 11.2 |
| 90A7596 | 0.1750 | 7.1000 | 6.7510 | 0.3490 | 47643644 | 1.965 | 11.2 | 1.937 | 11.1 |
| 90A-7597 | 0.1715 | 7.0926 | 6.7492 | 0.3434 | 46879161 | 1.933 | 11.3 | 1.906 | 11.1 |
| **Mean** | **0.1750** | | | **0.3534** | **48247721** | **1.990** | **11.4** | **1.962** | **11.2** |
| **S.D** | **0.0057** | | | **0.0119** | **1627691** | **0.067** | **0.2** | **0.066** | **0.1** |

a) dpm/gram dose solution = 136,514,738
b) mg 2,4-D/ml dose solution = 5.63
c) mg TIPA/g dose solution = 5.55

Specific activity of $^{14}$C-TIPA in dose solution = 136,514,738 dpm/5.55 mg TIPA or 24,597 dpm/µg TIPA.

Table 2. Concentration of $^{14}$C-TIPA in the Plasma of Rats Following A Single Oral Dose of 10 mg 2,4-D/kg & 10.7 mg $^{14}$C-TIPA/kg

| Sampling Time [hr] | 90A-7594 | 90A-7599 | 90A-7596 | 90A-7597 | Mean | S.D |
|---|---|---|---|---|---|---|
| 0.25 | 5.1129 | 5.7775 | 3.9032 | 3.1237 | 4.4793 | 1.1911 |
| 0.5 | 4.6674 | 4.7626 | 3.6279 | 4.1123 | 4.2926 | 0.5278 |
| 0.75 | 4.1642 | 3.9190 | 3.3259 | 3.7249 | 3.7835 | 0.3541 |
| 1.0 | 3.7131 | 3.0468 | 3.2840 | 3.4680 | 3.3780 | 0.2822 |
| 1.5 | 2.4694 | 2.7092 | 2.4405 | 2.3709 | 2.4975 | 0.1471 |
| 2.0 | 1.8321 | 1.9173 | 1.8612 | 2.0688 | 1.9199 | 0.1054 |
| 4.0 | 0.9843 | 0.9434 | 0.8806 | 0.7887 | 0.8993 | 0.0852 |
| 6.0 | 0.6265 | 0.7167 | 0.5611 | 0.6348 | 0.6348 | 0.0638 |
| 8.0 | 0.5721 | 0.4445 | 0.4808 | 0.5293 | 0.5067 | 0.0558 |
| 12.0 | 0.3399 | 0.2601 | 0.2962 | 0.2774 | 0.2934 | 0.0343 |
| 18.0 | 0.2349 | 0.1770 | 0.1875 | 0.1869 | 0.1966 | 0.0260 |
| 24.0 | 0.2079 | 0.1277 | 0.1272 | 0.1033 | 0.1415 | 0.0457 |
| 48.0 | 0.0935 | 0.0766 | 0.0687 | 0.0725 | 0.0778 | 0.0109 |
| 72.0 | 0.0620 | 0.0549 | 0.0617 | 0.0625 | 0.0603 | 0.0036 |

* µg equivalent $^{14}$C-TIPA/g plasma based one 24597 dpm/µg TIPA

Table 3. Distribution of Radioactivity Recovered in Male Rats 72 hours Following A Single Oral Dose of 10 mg 2,4-D/kg & 10.7 mCi $^{14}$C-TIPA/kg.

Percent of Administered Dose

| | 90A-7594 | 90A-7599 | 90A-7596 | 90A-7597 | Mean | S.D |
|---|---|---|---|---|---|---|
| Urine | 84.45 | 84.78 | 81.82 | 84.23 | 83.32 | 1.35 |
| Feces | 4.57 | 5.04 | 6.85 | 4.89 | 5.34 | 1.03 |
| $^{14}CO_2$ | 4.23 | 3.90 | 3.85 | 3.88 | 3.97 | 0.18 |
| Tissue + Carcass | 0.77 | 0.86 | 0.91 | 0.70 | 0.81 | 0.09 |
| Final Cage Wash | 1.24 | 0.64 | 0.94 | 0.38 | 0.80 | 0.37 |
| Total | 95.26 | 95.22 | 94.37 | 94.08 | 94.73 | 0.60 |

12

**Table 4. Concentration of Radioactivity in the Tissues of Male Rats 72 hours Following Single Oral Dose of 10 mg 2,4-D/kg & 10.7 mg $^{14}$C-TIPA/kg.**

**Percent of Administered Dose/ g Tissue**

| | 90A-7594 | 90A-7599 | 90A-7596 | 90A-7597 | Mean | S.D |
|---|---|---|---|---|---|---|
| **Carcass** | 0.0034 | 0.0031 | 0.0033 | 0.0030 | **0.0032** | 0.0002 |
| **Kidneys** | 0.0093 | 0.0067 | 0.0072 | 0.0073 | **0.0076** | 0.0011 |
| **Liver** | 0.0200 | 0.0207 | 0.0186 | 0.0211 | **0.0201** | 0.0011 |
| **Perirenal Fat** | 0.0026 | 0.0033 | 0.0018 | 0.0033 | **0.0028** | 0.0007 |
| **Skin** | 0.0050 | 0.0075 | 0.0087 | 0.0049 | **0.0065** | 0.0019 |

**Table 5. Concentration of Radioactivity in the Tissues of Male Rats 72 hours Following Single Oral Dose of 10 mg 2,4-D/kg & 10.7 mg $^{14}$C-TIPA/kg**

**Percent of Administered Dose**

| | 90A-7594 | 90A-7599 | 90A-7596 | 90A-7597 | Mean | S.D |
|---|---|---|---|---|---|---|
| **Carcass** | 0.400 | 0.379 | 0.378 | 0.357 | **0.379** | 0.018 |
| **Kidneys** | 0.011 | 0.009 | 0.009 | 0.009 | **0.010** | 0.001 |
| **Liver** | 0.132 | 0.131 | 0.109 | 0.132 | **0.126** | 0.011 |
| **Perirenal Fat** | 0.002 | 0.001 | <.001 | 0.001 | **0.001** | 0.001 |
| **Skin** | 0.0228 | 0.339 | 0.415 | 0.196 | **0.295** | 0.101 |
| **Total** | 0.773 | 0.859 | 0.911 | 0.695 | **0.810** | 0.095 |

**Table 6. Amount of $^{14}$C-TIPA and 2,4-D Excreted in the Urine Post-Dosing of A Single Oral Dose of 10 mg 2,4-D/kg & 10.7 mg $^{14}$C-TIPA/kg.**

| Collection Interval | Average Urinary Volume [g] | Urinary TIPA | | | Urinary 2,4-D | | |
|---|---|---|---|---|---|---|---|
| | | TIPA [µg/g] | $^{14}$C [µg eq/g] | TIPA ± $^{14}$C | Conc. [µg/g] | Amount [µg] | % Dose |
| 0 - 6 hr | 2.204[a] | 473 ± 7[b] | 495[c] | 95%[d] | 357[b] | 787 | 39.5[e] |
| 6 - 12 hr | 4.030 | 42 ± 3 | 52 | 80% | 153 | 617 | 31.0 |
| | | | | | Total 0 - 12 hr | | 70.5[f] |

a) Average urine of urine specimens excreted by three rats during this interval.

b) Concentration of TIPA and 2,4-D in pooled urine samples determined by GC/MS.

c) Concentration of $^{14}$C-TIPA based on concentration of radioactivity in pooled sample. Specific activity of $^{14}$C-TIPA was 24,597 dpm/µg $^{14}$C-TIPA.

d) Percentage of radioactivity accounted for by TIPA [TIPA/Total$^{14}$C-TIPA] x 100.

e) Average dose of 2,4-D was 1990µg [Table 1].

f) In a metabolism study with $^{14}$C-2,4-D acid, 69.1±13.1 % of a 1 mg oral dose was excreted by male rats during the first 12 hr post-dosing.

**Table 7. Radioactivity Excreted in the Urine of Rats Administered A Single Oral Dose of 10 mg 2,4-D/kg & 10.7 mg $^{14}$C-TIPA/kg.**

Percent Administered Dose

| Collection Interval | 90A-7594 | 90A-7599 | 90A-7596 | 90A-7597 | Mean | S.D |
|---|---|---|---|---|---|---|
| 0-6 hr Urine | 55.93 | 46.68 | 56.80 | 51.59 | | |
| 0-6 hr Cage Rinse | 10.78 | 18.30 | 12.94 | 18.20 | | |
| **Urine + Rinse** | **66.71** | **64.98** | **69.74** | **69.79** | **67.81** | 2.37 |
| 6-12 hr Urine | 12.48 | 11.51 | 8.09 | 8.72 | | |
| 6-12 hr Cage Rinse | 1.03 | 2.26 | 1.15 | 1.51 | | |
| **Urine + Rinse** | **13.51** | **13.77** | **9.24** | **10.23** | **11.69** | 2.29 |
| 12-24 hr Urine | 2.72 | 4.72 | 1.67 | 2.98 | | |
| 12-24 hr Cage Rinse | 0.25 | 0.45 | 0.17 | 0.32 | | |
| **Urine + Rinse** | **2.97** | **5.17** | **1.84** | **3.30** | **3.32** | 1.38 |
| 24-48 hr Urine | 0.77 | 0.57 | 0.57 | 0.49 | | |
| 24-48 hr Cage Rinse | 0.09 | 0.06 | 0.08 | 0.10 | | |
| **Urine + Rinse** | **0.86** | **0.63** | **0.65** | **0.59** | **0.68** | 0.12 |
| 48-72 hr Urine | 0.31 | 0.16 | 0.28 | 0.25 | | |
| 48-72 hr Cage Rinse | 0.09 | 0.07 | 0.07 | 0.07 | | |
| **Urine + Rinse** | **0.40** | **0.23** | **0.35** | **0.32** | **0.33** | 0.07 |
| **TOTAL** | **84.45** | **84.78** | **81.82** | **84.23** | **83.82** | 1.35 |

**Table 8. Radioactivity Excreted in the Feces of Rats Administered A Single Oral Dose of 10 mg 2,4-D/kg & 10.7 mg $^{14}$C-TIPA/kg.**

Percent Administered Dose

| Collection Interval | 90A-7594 | 90A-7599 | 90A-7596 | 90A-7597 | Mean | S.D |
|---|---|---|---|---|---|---|
| 0 - 24 hr | 4.20 | 4.56 | 5.38 | 3.93 | 4.52 | 0.63 |
| 24 - 48 hr | 0.25 | 0.40 | 0.98 | 0.39 | 0.51 | 0.32 |
| 48 - 72 hr | 0.12 | 0.08 | 0.49 | 0.57 | 0.32 | 0.25 |
| TOTAL | 4.57 | 5.04 | 6.85 | 4.89 | 5.34 | 1.03 |

**Table 9. Radioactivity Excreted As $^{14}CO_2$ in Rats Administered A Single Oral Dose of 10 mg 2,4-D/kg & 10.7 mg $^{14}$C-TIPA/kg.**

Percent Administered Dose

| Collection Interval | 90A-7594 | 90A-7599 | 90A-7596 | 90A-7597 | Mean | S.D |
|---|---|---|---|---|---|---|
| 0 - 12 hr | 3.62 | 3.39 | 3.35 | 3.38 | 3.44 | 0.12 |
| 12 - 24 hr | 0.42 | 0.33 | 0.29 | 0.31 | 0.34 | 0.06 |
| 24 - 36 hr | 0.10 | 0.11 | 0.12 | 0.12 | 0.11 | 0.01 |
| 36 - 48 hr | 0.09 | 0.07 | 0.09 | 0.07 | 0.08 | 0.01 |
| 48 - 72 hr | 0.07 | 0.05 | 0.08 | 0.06 | 0.07 | 0.01 |
| TOTAL | 4.23 | 3.90 | 3.85 | 3.88 | 3.97 | 0.18 |

# END